Familial Mediterranean fever in northwest of Iran (Ardabil): the first global report from Iran

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Familial Mediterranean fever (FMF), which is the prototype of the hereditary periodic fever syndromes, is common in the countries around the Mediterranean Sea. Considering its geographical position in the northwest of Iran, with its population of Turkish origin and its vicinity to the Mediterranean Sea, the incidence of FMF should be high in Ardabil. The goal of this study was to introduce FMF as a disease with significant outbreak in this area.

Based on the Tel-Hashomer criteria, patients suffering from FMF were collected from private clinics together with the medical records of adult and pediatric rheumatology clinics. Of 112 total patients determined, 74 were studied. All of the patients were interviewed and completed a questionnaire.

Familial Mediterranean fever was common among children under 18 years (76%), and it was more common in males than females (M/F 1.17). Abdominal pain was the most common complaint (74%) and abdominal pain and fever (95% and 84%, respectively) were the main clinical symptoms. The average duration of pain was 12-72 hours and the average recovery (attack-free period) was from one week to one month (63.5%). The majority of the patients had hospital admission for diagnostic work-up (85%) and some (32%) had undergone surgical operation erroneously; 92% of the patients had taken medications with incorrect diagnosis; and 20% had positive familial history of FMF. Fifty percent of the patients' parents were first-degree relatives and in 59.5% delay in diagnosis was more than three years.

It seems that FMF is more common in the Northwest of Iran than previously thought, although physicians are not familiar with it.

The common age for manifestation of this disease is under 18 years and its presentation after the age of 40 years is very rare.

Key words: periodic fever syndromes, familial Mediterranean fever, colchicine.

Familial Mediterranean fever (FMF) is the most common form of the hereditary periodic fever syndromes, which has autosomal recessive pattern and presents with self-limited periodic fever and serositis in its classic form[1,2]. Jewish, Armenian, Arab and Turkish people, i.e. people of Mediterranean origin, are affected by the disease[3]. MEFV is the responsible gene in this disease and it is located on the short arm of chromosome 16 near the gene responsible for polycystic kidney disease[2,4]. The mutation of this gene leads to defect in synthesis of a protein known as pyrin-marenostrin[5,6]. This protein, along with other proteins involved in cell death, has a role in control and regression of the inflammatory cycle. Its deficiency also leads to continuous inflammation, inflammatory explosion and finally to febrile serositis[2,7,8].

More than 50 mutations in the gene on chromosome 16 have been recorded[7], but there are five main mutations in people affected by FMF, and 91% of the patients have one of these five mutations, which include: M694V (common version), M680I, M694I, E148Q and V720S[6]. These various mutations explain the different phenotypes in FMF patients[9]. M694V mutation is interrelated with severe clinical presentation, more incidences in arthritis and its progression toward amyloidosis[10,11].

Cytokines like interleukin (IL)-2, IL-6, IL-8 and IL-10 have roles in the pathogenesis of the disease[12,13].

In the attack-free period, the existence of protracted subacute clinical inflammation has been described[14]. Abdominal pain because of sterile serositis is the most common clinical symptom in FMF[5,15]. The pain may be so severe that it may mimic acute abdomen. Chest pain has been reported in more than 50% of the patients[5]. The classic arthritis in FMF is a self-limited monoarthritis; half of patients have arthralgia, but destructive arthritis and sacroiliitis are very rare[16,17]. Myalgia has been reported in FMF in less than 20% of patients, typically lasting for less than two days[5]. The most common myalgia that has been described in FMF is activity-dependent myalgia (18%)[18].

Skin rash in FMF is an erysipelas-like erythema[19]. Aseptic meningitis, headache, pericarditis and hematuria and orchitis are other symptoms of this disease[4-6,9,20].

The only truly accepted diagnostic method is the analysis of the MEFV gene[5,21], though "reverse hybridization" and "nuclei and nucleolar organizing regions" are other newly introduced means of diagnosis[22,23].

Familial Mediterranean fever association with some diseases such as juvenile idiopathic arthritis (JIA), Addison, inflammatory bowel disease, chronic myelogenous leukemia (CML), *Helicobacter pylori* infection and Behçet's disease has been described[5,24-30].

Colchicine is the only effective treatment; this medication is effective in 95% of patients but 5% show resistance[5,31]. Today, intravenous colchicine[32], interferon alpha administration[33], and tumor necrosis factor (TNF) receptor blockers[34] have been used successfully in patients who were colchicine-nonresponsive.

Material and Methods

This is a descriptive study conducted in the northwest of Iran (Ardabil). We studied the medical records of these patients from adult and pediatric (under 18 years) rheumatology as well as some private clinics. In total, we obtained a list of 112 affected or suspected patients. Fifteen patients did not agree to participate, 20 had no address or phone number and 3 did not enter the study because of other diagnoses. Consequently, 74 patients were enrolled in the study.

We used Tel-Hashomer criteria for diagnosis of FMF. Tel-Hashomer criteria, with major and minor criteria, have been described as a diagnostic criterion of FMF. It is also very valuable in the areas where FMF is common. Major criteria include 1- Recurrent fever together with serositis, 2- AA amyloidosis without any other susceptible agent, and 3- Good response to continual treatment with colchicine. Minor criteria also include 1- recurrent fever, 2- Erysipelas-like erythema, and 3- Positive familial background. Two major criteria or two minor criteria along with one major criterion indicate definite diagnosis of disease. However, one major criterion with one minor indicates probable diagnosis of disease[4].

All had definitive Tel-Hashomer criteria, and they all completed a questionnaire. We abstracted age, gender, age of onset, periodicity, all symptoms and signs, parental consanguinity, family history, period of treatment, dosage of colchicine, clinical response, and side effects. According to subjective criteria, pain intensity was evaluated in a range of 1-10, with a score of 1-4 considered as mild pain, 5-7 as moderate pain and 8-10 as severe pain.

The collected data were analyzed with SPSS software.

Results

Of the 74 patients, 40 (54%) were male and 34 (46%) female. Eighty-four percent of the patients were in the pediatric group, among whom those aged 1-10 years were the most affected. The onset of symptoms was often in the childhood period (Table I).

Incidence of disease in the pediatric group was most common between 2-4 years of age and in adults between 25-30 years. Abdominal

Table I. Age at Onset of Clinical Presentation

Age	Number of patients	Percent
Infant	8	10.8%
1-10 yrs	36	48.7%
10-20 yrs	18	24.3%
20-40 yrs	10	13.5%
40-50 yrs	01	1.3%
50-55 yrs	1	1.3%
Total	74	100%

pain (74%) and chest pain (6.8%) were the main complaints among the patients. The other clinical complaints are listed in Table II.

Most of the patients (78%) had severe pain, 17.5% had moderate, and the remainder (4.5%) suffered from mild pain.

Table II. Main Complaints of Patients

Main complaint	Number of patients	Percent
Abdominal pain	55	74.3%
Chest pain	5	6.8%
Irritability	4	5.4%
Fever	4	5.4%
Respiratory discomfort	1	1.4%
Constipation	1	1.4%
Arthritis	1	1.4%
Arthralgia	1	1.4%
Headache	1	1.4%
Chill	1	1.4%
Total	74	100%

The average duration of pain was 12-72 hours in 76% of the patients. In 13.5%, it was more than 72 hours and in the remainder less than 12 hours. The average pain-free period was one week to one month (63.5%).

Systemic symptoms such as fever, chill, malaise and weakness were reported in 99% of the patients and symptoms of digestive tract were observed in 97%. Involvement of the other organs is shown in Figure 1.

The most common symptoms were abdominal pain (95%) and fever (84%) and the remainder are shown in Table III.

Three patients had goiter. One of them was euthyroid, another hypothyroid and the third hyperthyroid. Eye symptoms were blurred vision, conjunctivitis, erythema, and edema around the eye. Chest pain was noted in 24%, constipation in 42% and paresthesia in 22%.

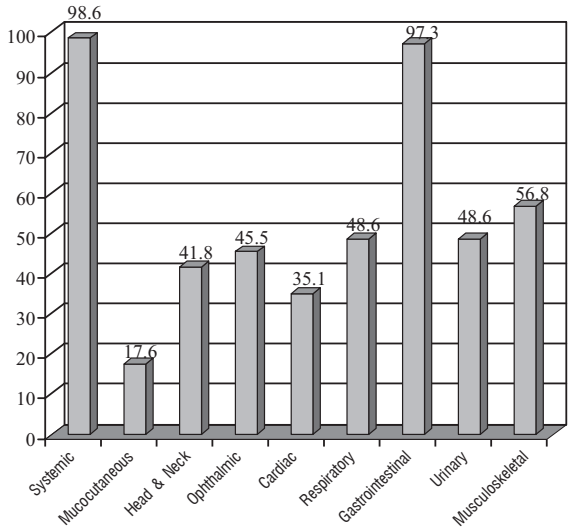

Fig. 1. Prevalence of organ involvement in patients.

Table III. Prevalence of Different Clinical Symptoms in Patients

Clinical symptoms	Percent	Number of patients
Fever	83.8	62
Anorexia	81.1	60
Chill	60.8	45
Weakness	59.9	44
Anathema	6.8	5
Exanthema	12.2	9
Headache	40.5	30
Blurred vision	8.1	6
Conjunctivitis	36.5	27
Palpitation	35.1	26
Respiratory distress	43.2	32
Chest pain	24.3	18
Nausea	71.6	53
Vomiting	63.5	47
Abdominal pain	94.6	70
Diarrhea	18.9	14
Constipation	41.9	31
Change in urine color	39.2	29
Dysuria	28.4	21
Myalgia	23	17
Arthralgia	37.8	28
Arthritis	23	17
Vertigo	28.4	21
Paresthesia	21.6	16
Tremor	6.8	5

All of the patients were of Turkish origin. Fifty-four percent of the patients had a history of hospital admission, 32% had undergone surgical operations with acute abdomen and laparotomy and 91% had taken wrong medications.

Antibiotics (38%), non-steroidal anti-inflammatory drugs (NSAIDS) (35%) and antipyretics (30%) were the most commonly used drugs. Emergency surgical operation (31%) and infectious diseases such as parasitic infection (20%) were common mis-diagnoses.

Twenty percent had positive family history of FMF and 7% of their relatives had similar symptoms, but they had no medical evaluation. Parental consanguinity was present in 50% of the patients. The patients' response to colchicine was good in 78% (symptom-free), moderate in 5% (50% response) and poor in 4% (no response); the remainder of the patients were newly diagnosed and had not taken the drug for more than six months. Diarrhea was the common side effect of colchicine (24%).

Amyloidosis was present in 2.7% of the patients and resulted in death in two patients. There was no statistically significant relationship between sex and severity of disease (p=0.6). A statistically significant relationship was determined between arthritis and the pediatric age group (p=0.008). The relationships between arthralgia and chest pain in the pediatric group and fever in the adult group were also statistically significant (p=0.009, p=0.024, p=0.007, respectively).

Discussion

The first group of pediatric FMF cases (13 patients) from the northwest of Iran was reported by Salehzadeh et al.[35] at the Tehran International Pediatric Congress in 1994, and the present study is the second global report from this area. Geographical location, population of Turkish origin, proximity to Armenia and immigration are the main contributing reasons for its prevalence. Familial marriage (consanguinity) is another possible factor.

The high frequency of emergency operation, erroneously performed more than once in some patients, and various inappropriate medications given due to incorrect diagnosis indicate that it is still a largely unknown disease in Iran.

In this study, 84% of the patients were under the age of 20. Pain intensity is different, as reported in similar studies[5,6]. In this study, most of the patients complained of severe pain. The duration of each attack is usually 12-72 hours[5,6], which was also comparable with results in our patients. The pain-free interval also varies in the different studies[11]. The average attack-free interval of disease in our study was one week to one month, and then 1-2 months.

Fever is seen in all patients but it may be ignored[5]. In our study, fever was observed in 84% of the patients. Fever and abdominal pain are the common clinical symptoms in children and in adults[21]; 94.6% of our patients had abdominal pain. In our group, 4% had thyroid dysfunction and variation in thyroid size. This finding may be related to the onset of systemic amyloidosis coexistent with other auto-inflammatory disorders.

Myalgia has been reported in 20% of the patients[5], and 23% of our patients had activity-related myalgia. Joint involvements in the form of arthritis or arthralgia are seen in 50% of the patients[5]. In our study, the rate was higher, and in 1% of the patients, arthritis had developed as a destructive arthritis. Regarding the high incidence of joint involvement and its relation with the M694V mutation, this kind of mutation may be common in this region.

In the adult group, 2.7% of the patients were using opium as a pain-relieving agent. In 4% of the patients, response to colchicine was very poor although in some it could be related to inadequate dosage of drug, or to its interrupted use. Diarrhea was the common side effect of colchicine.

There is a relation between amyloidosis and sex, with a male predominance[11]. In our study, both patients with amyloidosis were male.

This study shows a large number of FMF patients from the northwest of Iran and indicates the high frequency of FMF in this region.

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